Please amend claim 15 as follows:

15. (amended) A method of killing an imported fire ant queen, comprising the step of contacting said fire ant queen with the pest eradication product of claim 1.

REMARKS

Status of the Claims

Claims 1-3, 6-9, and 12-19 are pending. Claims 1-3, 6-9, and 12-19 are rejected. Claims 1 and 15 are amended to overcome the rejections under 35 U.S.C §102(e) and §103(a); claims 7 and 12-14 are amended for reasons of clarity. Claims 2 and 6 are cancelled. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**"

The 35 U.S.C. §112, first and second paragraph rejections

Claims 6, 12, 13, 14, and 17-19 stand rejected under 35 U.S.C §112, first and second paragraphs, as being nonenabled and

indefinite because the specification does not disclose a repeatable process to obtain the monoclonal antibodies, hybridomas or phage display clones, and it is not clear that these items are readily available to the public. Applicants submit that the claimed biological materials are being deposited to obviate the rejection, and that evidence of said deposit will be forwarded to the Examiner upon receipt.

The 35 U.S.C §102(e) rejection

Claims 1, 3, 5 and 15 stand rejected under 35 U.S.C §102(e) as being anticipated by U.S. Patent No. 5,686,600 (**Carozzi** *et al.*). Applicants respectfully traverse this rejection.

The Examiner states that **Carozzi** teaches the use of a product to get rid of pests comprising an antibody that binds to the midgut region of a pest, and that these teachings anticipate the rejected claims. Applicants respectfully submit that the amendments to claims 1 and 15 overcome the rejection (the rejection of claim 5 is moot, because claim 5 was canceled in the Response to the Office Action mailed April 22, 2002). Claims 1 and 15 have been amended to incorporate limitations from claims 2 and 6, and now recite that the antibody directed against the microvilli in the midgut region of

an imported fire ant queen is secreted from a selected group of hybridomas. These hybridomas are not taught by **Carozzi**, so that **Carozzi** does not teach each and every element of the claims. Accordingly, Applicants respectfully request that the rejection of claims 1, 3, 5 and 15 under 35 U.S.C. §102(e) be withdrawn.

The 35 U.S.C. §103(a) rejection

Claims 1-3, 7-9 and 16 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,686,600 (**Carozzi** *et al.*) in view of U.S. Patent No. 5,837,242 (**Holliger** *et al.*) and U.S. Patent No. 5,870,852 (**Stanley**). This rejection is respectfully traversed.

The Examiner states that the claims are limited to fused antibodies or fragments thereof, which encompasses the prior art teachings; the present specification teaches a method for making an antibody fusion very similar to that taught by the prior art.

Applicants respectfully submit that when the claimed invention is considered as a whole, the prior art contains no teaching or suggestion that combining the elements of the invention would be desirable; in the absence of such a teaching or suggestion, the prior

cannot render the present claims obvious. Therefore, the invention as presently claimed is patentable over the cited references.

Carozzi teaches an antibody or antibody fragment that binds to a midgut antigen of insects, which may be fused to a toxin for the control of insect pests (see Abstract). The antibody or fragment is fused directly to a toxin, providing a region for binding to the insect gut, and a toxic region to effect killing of the targeted cell, and the targeted insect in turn (column 4, lines 6-10). **Carozzi** does not teach or suggest the particular antibodies secreted by the hybridoma lines recited in the present claims as amended. These hybridoma lines were selected for their secretion of antibodies that are able to bind midgut antigens of imported fire ant queens, but not of native fire ants. Example 1, and Table 1 therein, describe the production of hybridoma lines that secrete specific antibodies with binding specificity to the midgut microvilli of imported fire ant queens. Example 2 discloses the production of phage-displayed antibody fragments with specificity for midgut antigens of imported fire ant queens. **Carozzi** teaches the preparation of and screening for antibodies that bind antigens in the gut of only the target insect, such as an insect selected from a particular order, as opposed to

antigens in the mammalian gut, or antigens from plants (see column 2, lines 54-67, and column 3, lines 1-20). **Carozzi** does not teach or suggest preparing and screening for antibodies that differentiate in midgut antigen binding specificity between insects of the same genus, such as native versus imported fire ant species, in contrast to the present invention.

In addition, the present invention also discloses the fusion of an antibody or antibody fragment to a second antibody or antibody fragment, where the second antibody or antibody fragment has binding specificity for a toxin. The production of antibodies and phage-displayed antibody fragments having binding specificity for gelonin is described in Examples 3 and 4, respectively. Such a combination of two antibodies or fragments together that have different binding specificities for the pest midgut antigen and for a toxin is not contemplated nor suggested by **Carozzi**.

In consideration of the above comments, Applicants respectfully submit that no combination of the **Carozzi**, **Holliger** and **Stanley** references provide the requisite teaching or suggestions that would motivate a person having ordinary skill in this art to produce the claimed invention.

Holliger teaches the fusion of single chain fragments of antibodies from either the heavy or light chain variable region together to form a dimer. The single chain heavy and light chain fragments are fused together such that they cannot associate with each other to form an antigen binding site, but can associate with a complementary heavy or light chain fragment from a separate similarly fused dimer, which may be multivalent or have multispecificity (see Abstract). Dimers between fragments having different specificities may bind together to form two different binding sites having specificity for different antigens (bispecific antibodies or "diabodies"); see column 2, lines 55-67, column 3, lines 1-13, and Figure 2.

Holliger does not teach or suggest that the creation of bispecific antibodies would be useful for localizing a toxin to the midgut cells of a pest, by fusing an antibody or antibody fragment with binding specificity to a midgut antigen to a second antibody or fragment with binding specificity for a toxin. **Holliger** makes no reference to pest control whatever, providing no motivation to combine the elements of **Holliger** with the teachings of **Carozzi** to arrive at the claimed invention.

In addition, the teachings of **Holliger** are different from the disclosed elements of the present invention. In **Holliger**, a dimer between two fused single chain antibody fragments must be able to bind to another such dimer in order to form a functional antigen-binding site. In contrast, the present claims recite an entire antibody secreted by a hybridoma, or an antibody fragment derived from a phage display library. In the specification, "antibody fragment" or "Fab" is defined as an immunoglobulin-based recognition unit of minimum size comprised of variable region segments from immunoglobulin heavy and light chains that exhibit high affinity to target antigens (see page 11, lines 7-10). Thus, the claimed antibody or fragment thereof has a functional antigen binding site before being fused to either a toxin or a second antibody or antibody fragment, which also has a functional antigen binding site (see Example 4). The present specification also does not describe the use of peptide linkers between heavy and light chain fragments. The structure of the bispecific antibodies taught by **Holliger**, as well as the methods of producing them, are therefore materially different from the antibodies and antibody fragments disclosed in the present specification and claims.

Stanley teaches an extermination system for killing fire ants by injecting hot water into a fire ant mound (see Abstract). This system kills fire ants by external contact with scalding water, which teaches away from the Applicants' claims, which describe a targeted destruction of pests through delivery of a toxin internally to the midgut via fusion of the toxin to a midgut-specific antibody or antibody fragment.

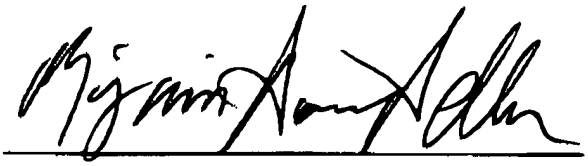
In summary, none of the teachings or suggestions of **Carozzi**, **Holliger** or **Stanley**, either taken alone or in combination, provide the necessary motivation to one skilled in the art to combine the elements of the invention as recited in the claims as amended. **Carozzi** does not teach or suggest the fusion of antibodies or antibody fragments of different specificities together, or an antibody or antibody fragment with binding specificity to a toxin. **Holliger** makes no reference to the use of bispecific antibodies in a method of pest eradication or control, and teaches fused antibody fragments with dual binding specificity that are materially different in structure and method of production from the elements disclosed in the present specification and claims as amended. **Stanley** teaches a method of killing fire ants that teaches away from the method of the

claimed invention. Therefore, the cited references do not provide any teaching or suggestion to one skilled in the art to combine the elements of the claimed invention. Accordingly, Applicants respectfully request that the rejection of claims 1-3, 7-9 and 16 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Final Office Action mailed December 10, 2002. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution. Should any additional fees be due, please debit Deposit Account 07-1185.

Respectfully submitted,

Date: Feb 13, 2003



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend claim 1 as follows:

1. (twice amended) A pest eradication product comprising an antibody or an antibody fragment directed against the microvilli in the midgut region of ~~a pest~~ an imported fire ant queen, wherein said antibody or antibody fragment is fused to a toxin, wherein said antibody is secreted from a hybridoma selected from the group consisting of FA1, FA4, FA7, FA8, FA9, FA10, FA13, FA14, FA15, and FA17.

Please cancel claims 2 and 6.

Please amend claim 7 as follows:

7. (twice amended) A pest eradication product comprising a first antibody or a fragment thereof directed against the microvilli in the midgut region of a pest, wherein said first antibody or fragment thereof is fused to a second antibody or a fragment thereof directed against an antigenic epitope of a toxin, and a toxin.

Please amend claim 12 as follows:

12. (twice amended) The pest eradication product of claim 7, wherein said antibody directed against said microvilli is secreted from a hybridoma selected from the group consisting of FA1, FA4, FA7, FA8, FA9, FA10, FA13, FA14, FA15, and FA17.

Please amend claim 13 as follows:

13. (twice amended) The pest eradication product of claim 7, wherein said second antibody directed against said antigenic epitope of a toxin is secreted from a hybridoma selected from the group consisting of G1, G2, G3, G4, G5, G6, and G7.

Please amend claim 14 as follows:

14. (twice amended) The pest eradication product of claim 7, wherein said antibody fragment directed against said antigenic epitope of a toxin is derived from a phage display library clone selected from the group consisting of pComb3/Fab(6) and pComb3/Fab(47).

Please amend claim 15 as follows:

15. (amended) A method of killing ~~a pest~~ an imported fire ant queen, comprising the step of contacting said ~~pest~~ fire ant queen with the pest eradication product of claim 1.